CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074475

Trade Name : TERFENADINE TABLETS USP

Generic Name: Terfenadine Tablets USP 60mg

Sponsor : Baker Norton Pharmaceuticals, Inc.

Approval Date: January 3, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074475

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	**X**			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	**X**			
Medical Review(s)				
Chemistry Review(s)	**X**			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	**X**			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 0744575

APPROVAL LETTER

ANDA 74-475

JAN 3 1997

Baker Norton Pharmaceuticals, Inc.
Attention: Jane H. Hsiao, Ph.D.
4400 Biscayne Boulevard
Miami, FL 33137

Dear Madam:

This is in reference to your abbreviated new drug application dated February 25, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terfenadine Tablets USP, 60 mg.

Reference is also made to our letter dated January 31, 1996 granting tentative approval to this abbreviated application, and to your amendments dated November 14, 1996 and January 2, 1997.

The application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act to U.S. patent number 4,254,129, which expires on April 10, 1999. You notified Marion Merrell Dow, Inc. (now Hoechst Marion Roussel) of the patent certification and were sued for patent infringement (Marion Merrell Dow Inc. and Merrell Dow Pharmaceuticals, Inc. v. Baker Norton Pharmaceuticals, Inc., Civil Action No.94-1245).

The 30 month period, provided for in Section 505 (j)(4)(B)(iii)of the Act, during which FDA was prohibited from approving your application, has expired. We have therefore completed the final review of this abbreviated application and have concluded that the application meets the requirements of Section 505(j) of the Act. Accordingly, the application is approved.

The Division of Bioequivalence has determined your Terfenadine Tablets USP, 60 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Seldane Tablets, 60 mg of Hoechst Marion Roussel, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

1-3-97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 0744575

CHEMISTRY REVIEWS

Addendum to Review #3

ANDA 74-475

APPLICANT
Baker Norton Pharmaceuticals, Inc.
Attention: Edgar W. Mitchell, Ph.D.
4400 Biscayne Boulevard
Miami, FL 33137

DRUG PRODUCT **Terfenadine Tablets USP**

COMMENTS
Changes made in response to tentative approval letter are acceptable.

AMENDMENTS AND OTHER DATES
Amendment Date November 14, 1996
Telephone Amendment Date January 2, 1997

CONCLUSIONS AND RECOMMENDATIONS
Approvable, pending Review of the Patent Issues.

NOTE: In the ANDA, the firm provided a S.O.P (#0200.013) which stated that the Q.A. verifies that materials/products which are covered by USP/NF monographs are tested for the criteria specified in the monograph. However, the firm was requested to provide a commitment to comply with the current USP tests and specifications for terfenadine raw material.

The firm provided revised specification and a certificate of analysis for one of the batches of terfenadine (BNP lot #R60902-11) together with a commitment to comply with the current USP tests and specifications.

Updated specifications for the active drug substance, terfenadine, comply with USP 23, Supplement 4.

REVIEWER:
U. Atwal

DATE COMPLETED:
December 2, 1996
Revised: January 2, 1997

firm requested to verify that drug substance meets specifications in USP-Supplement 4. Data in application was not specific on this point. ap

cc: ANDA 74-475
DUP Jacket
Division File
Field Copy

Endorsements:
HFD-623/U. Atwal, Ph.D./ 1/2/97
HFD-623/V. Sayeed, PhD./ 1/2/97
X:\74475.RV3
F/T by /

1. CHEMISTRY REVIEW NO 3 2. ANDA 74-475

3. NAME AND ADDRESS OF APPLICANT
Baker Norton Pharmaceuticals, Inc.
Attention: Jane Hsiao, Ph.D.
8800 Northwest 36th Street
Miami, FL 33178

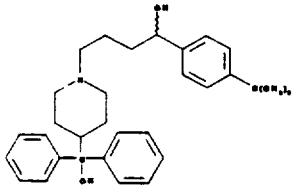
4. LEGAL BASIS FOR SUBMISSION Seldane® of Marion Merrell Dow
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME N/A
7. NONPROPRIETARY NAME **Terfenadine Tablets USP**
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

February 25, 1994	Date of application.
September 2, 1994	CMC/label NA letter
October 25, 1994	CMC/label amendment
November 16, 1994	Bio NA letter
December 16, 1994	Bio amendment
February 2, 1995	CMC/label NA letter
June 5, 1995	CMC/label amendment; **this review**

10. PHARMACOLOGICAL CATEGORY Antihistamine 11. Rx or OTC Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM oral tablet 14. POTENCY 60 mg

15. CHEMICAL NAME AND STRUCTURE
Terfenadine USP $C_{32}H_{41}NO_2$; M.W. = 471.68
α-(*p*-tert-Butylphenyl)-4-(hydroxydiphenylmethly)
-1-piperidine-butanol. CAS [50679-08-8]



16. RECORDS AND REPORTS N/A

17. COMMENTS All chemistry issues are adequately addressed.

18. CONCLUSIONS AND RECOMMENDATIONS **Approval** pending EER
pending labeling

19. REVIEWER: Jon E. Clark DATE COMPLETED: June 22, 1995

cc: ANDA 74-475
DUP Jacket
Division File
Field Copy

Endorsements:
HFD-623/J. Clark/ 6-23-95
HFD-623/R. Kishore, PhD./ 6-26-95
X:\WPFILE\BRANCH1\CLARK\N74475R2
F/T by /

Release specification revised in amendment of August 2, 1995
6-22-95
4-5-95

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 0744575

FINAL PRINTED LABELING

LOT NO.
EXP.

BAKER NORTON PHARMACEUTICALS, INC.®

NDC 0575-6401-05

TERFENADINE TABLETS USP

60 mg

500 tablets

CAUTION: Federal (USA) law prohibits dispensing without prescription.

EACH TABLET CONTAINS:
TERFENADINE.....60 mg

Dispense in a tight, light-resistant container with child-resistant closure.

USUAL ADULT DOSAGE: ONE TABLET TWICE DAILY.
See accompanying product information.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F)

KEEP TIGHTLY CLOSED.
PROTECT FROM MOISTURE.

Mfg. by:
Baker Norton
Pharmaceuticals, Inc.
Miami, FL 33178

3 05756 40105 8

INCLUDE ONE OF THE ENCLOSED PATIENT INSERTS WITH EACH PACKAGE DISPENSED.

PEEL DOWN

L001024
Rev. 9502

PATIENT INFORMATION
Terfenadine Tablets USP
60 mg

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How Do I Store Terfenadine?

Terfenadine should be stored in a tightly closed container, in a cool place, out of direct sunlight.

It should be kept away from children.

Patient Information as of February 1995

Manufactured by

BAKER NORTON PHARMACEUTICALS, INC.

Miami, FL 33178 L001024 REV 9502

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In rare cases, terfenadine has caused IRREGULAR HEARTBEATS which may cause serious problems like fainting, dizziness, cardiac arrest, or death. In these rare cases, this occurred when terfenadine was taken:

- in more than the recommended dose (Remember, do not take more often than one tablet every twelve hours.);
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How Do I Store Terfenadine?

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It should be kept away from children.

Patient Information as of February 1995

Manufactured by

BAKER NORTON PHARMACEUTICALS, INC.®

Miami, FL 33178 L001024 REV 9502

PATIENT INFORMATION
Terfenadine Tablets USP
60 mg

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13

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How Do I Take Terfenadine?

- Take terfenadine only as needed when you have symptoms of seasonal allergy or hay fever.
- The recommended dose of terfenadine is one tablet taken twice a day. **DO NOT TAKE MORE OFTEN THAN ONE TABLET EVERY TWELVE HOURS**
- Follow any other instructions your doctor gives you.

What Are The Important Warnings About Using Terfenadine?

WARNING: DO NOT USE TERFENADINE IF YOU ARE USING KETOCONAZOLE (NIZORAL), ITRACONAZOLE (SPORANOX), ERYTHROMYCIN, CLARITHROMYCIN (BIAXIN), OR TROLEANDOMYCIN (TAO). IF YOU HAVE ANY LIVER OR HEART PROBLEMS, TALK TO YOUR DOCTOR BEFORE YOU USE TERFENADINE.

Do not use terfenadine with any other prescription or nonprescription medicines without first talking to your doctor and pharmacist.

If you faint, become dizzy, have any unusual heartbeats, or any other unusual symptoms while using terfenadine, contact your doctor.

L001024 REV 9502

If you become pregnant or are nursing a baby, talk to your doctor about whether you should take terfenadine. Your doctor will decide whether you should take terfenadine based on the benefits and the risks.

What Are the Risks of Using Terfenadine?

The side effects which occur most often are headaches and mild stomach or intestinal problems.

In rare cases, terfenadine has caused IRREGULAR HEARTBEATS which may cause serious problems like fainting, dizziness, cardiac arrest, or death. In these rare cases, this occurred when terfenadine was taken:

- in more than the recommended dose (Remember, do not take more often than one tablet every twelve hours.);
- with the antifungal drugs ketoconazole (Nizoral) or itraconazole (Sporanox);
- with the antibiotic drugs erythromycin, clarithromycin (Biaxin), or troleandomycin (TAO);
- by patients with serious liver disease.

How Do I Store Terfenadine?

Terfenadine should be stored in a tightly closed container, in a cool place, out of direct sunlight.

It should be kept away from children.

Patient Information as of February 1995

Manufactured by

BAKER NORTON PHARMACEUTICALS, INC.

Miami, FL 33178 L001024 REV 9502

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INBOOK

Prescribing information as of February 1995

TERFENADINE TABLETS USP

60 mg

WARNING BOX

QT INTERVAL PROLONGATION/ VENTRICULAR ARRHYTHMIA

RARE CASES OF SERIOUS CARDIOVASCULAR ADVERSE EVENTS, INCLUDING DEATH, CARDIAC ARREST, TORSADES DE POINTES, AND OTHER VENTRICULAR ARRHYTHMIAS, HAVE BEEN OBSERVED IN THE FOLLOWING CLINICAL SETTINGS, FREQUENTLY IN ASSOCIATION WITH INCREASED TERFENADINE LEVELS WHICH LEAD TO ELECTROCARDIOGRAPHIC QT PROLONGATION:

1. **CONCOMITANT ADMINISTRATION OF KETOCONAZOLE OR ITRACONAZOLE**
2. **OVERDOSE, INCLUDING SINGLE DOSES AS LOW AS 360 MG**
3. **CONCOMITANT ADMINISTRATION OF CLARITHROMYCIN, ERYTHROMYCIN, OR TROLEANDOMYCIN**
4. **SIGNIFICANT HEPATIC DYSFUNCTION**

TERFENADINE IS CONTRAINDICATED IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN, CLARITHROMYCIN, OR TROLEANDOMYCIN, AND IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION.

DO NOT EXCEED RECOMMENDED DOSE.

IN SOME CASES, SEVERE ARRHYTHMIAS HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. SYNCOPE IN PATIENTS RECEIVING TERFENADINE SHOULD LEAD TO DISCONTINUATION OF TREATMENT AND FULL EVALUATION OF POTENTIAL ARRHYTHMIAS.

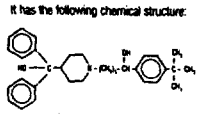
(See CONTRAINDICATIONS, WARNINGS, CLINICAL PHARMACOLOGY, AND PRECAUTIONS: DRUG INTERACTIONS.)

DESCRIPTION

Terfenadine is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, povidone, and sodium bicarbonate.

Terfenadine is a histamine H1-receptor antagonist with the chemical name α-[*p*-*tert*-Butylphenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol. The molecular weight is 471.68. The molecular formula is $C_{32}H_{41}NO_2$.

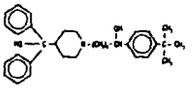
It has the following chemical structure:



Terfenadine occurs as a white to off-white crystalline powder. It is freely soluble in

alpha-(4-tert-Butylphenyl)-4-(hydroxydiphenylmethyl)-1-piperidinebutanol. The molecular weight is 471.68. The molecular formula is $C_{32}H_{41}NO_2$.

It has the following chemical structure:



Terfenadine occurs as a white to off-white crystalline powder. It is freely soluble in chloroform, soluble in alcohol and methanol, and slightly soluble in water.

CLINICAL PHARMACOLOGY

Terfenadine is chemically distinct from other antihistamines.

Histamine skin wheal studies have shown that terfenadine in single and repeated doses of 60 mg in 64 subjects has an antihistaminic effect beginning at 1-2 hours, reaching its maximum at 3-4 hours, and lasting in excess of 12 hours. The correlation between response on skin wheal testing and clinical efficacy is unclear. The four best controlled and largest clinical trials each lasted 7 days and involved about 1,000 total patients in comparisons of terfenadine (60 mg b.i.d.) with an active drug (chlorpheniramine, 4 mg t.i.d.; dexchlorpheniramine, 2 mg t.i.d.; or clemastine 1 mg b.i.d.). About 50-70% of terfenadine or other antihistamine recipients had moderate to complete relief of symptoms, compared with 30-50% of placebo recipients. The frequency of drowsiness with terfenadine was similar to the frequency with placebo and less than with other antihistamines. None of these studies showed a difference between terfenadine and other antihistamines in the frequency of anticholinergic effects. In studies which included 52 subjects in whom EEG assessments were made, no depressant effects have been observed.

Animal studies have demonstrated that terfenadine is a histamine H1-receptor antagonist. In these animal studies, no sedative or anticholinergic effects were observed at effective antihistaminic doses. Radioactive disposition and autoradiographic studies in rats and radioligand binding studies with guinea pig brain H1-receptors indicate that, at effective antihistamine doses, neither terfenadine nor its metabolites penetrate the blood brain barrier well.

On the basis of a mass balance study using 14C labeled terfenadine the oral absorption of terfenadine was estimated to be at least 70%. Terfenadine itself undergoes extensive (99%) first pass metabolism to two primary metabolites, an active acid metabolite and an inactive dealkylated metabolite. Therefore, systemic availability of terfenadine is low under normal conditions, and parent terfenadine is not normally detectable in plasma at levels >10 ng/mL. Although in rare cases there was measurable plasma terfenadine in apparently normal individuals without identifiable risk factors, the implications of this finding with respect to the variability of terfenadine metabolism in the normal population cannot be assessed without further study. Further studies of terfenadine metabolism in the general population are pending. From information gained in the 14C study it appears that approximately forty percent of the total dose is eliminated renally (40% as acid metabolite, 30% dealkyl metabolite, and 30% minor unidentified metabolites). Sixty percent of the dose is eliminated in the feces (50% as the acid metabolite, 2% unchanged terfenadine, and the remainder as minor unidentified metabolites). Studies investigating the effect of hepatic and renal insufficiency on the metabolism and excretion of terfenadine are incomplete. Preliminary information indicates that in cases of hepatic impairment, significant concentrations of unchanged terfenadine can be detected with the rate of acid metabolite formation being decreased. A single-dose study in patients with hepatic impairment revealed increased parent terfenadine and impaired metabolism, suggesting that additional drug accumulation may occur after repetitive dosing in such patients. Terfenadine is contraindicated for use in patients with significant hepatic dysfunction. (See **CONTRAINDICATIONS** and **WARNINGS**.) In subjects with normal hepatic function unchanged terfenadine plasma concentrations have not been detected. **Elevated levels of parent terfenadine, whether due to significant hepatic dysfunction, concomitant medications, or overdose, have been associated with QT interval prolongation and serious cardiac adverse events.** (See **CONTRAINDICATIONS** and **WARNINGS**.) In controlled clinical trials in otherwise normal patients with rhinitis, small increases in QTc interval were observed at doses of 60 mg b.i.d. In studies at 300 mg b.i.d. a mean increase in QTc of 10% (range -4% to +30%) (mean increase of 46 msec) was observed.

Data have been reported demonstrating

increased parent terfenadine and impaired metabolism, suggesting that additional drug accumulation may occur after repetitive dosing in such patients. Terfenadine is contraindicated for use in patients with significant hepatic dysfunction. (See **CONTRAINDICATIONS** and **WARNINGS**.) In subjects with normal hepatic function unchanged terfenadine plasma concentrations have not been detected. Elevated levels of parent terfenadine, whether due to significant hepatic dysfunction, concomitant medications, or overdose, have been associated with QT interval prolongation and serious cardiac adverse events. (See **CONTRAINDICATIONS** and **WARNINGS**.) In controlled clinical trials in otherwise normal patients with rhinitis, small increases in QTc interval were observed at doses of 60 mg b.i.d. In studies at 300 mg b.i.d. a mean increase in QTc of 10% (range -4% to +30%) (mean increase of 46 msec) was observed.

Data have been reported demonstrating that compared to young subjects, elderly subjects experience a 25% reduction in clearance of the acid metabolite after single-dose oral administration of 120 mg. Further studies are necessary to fully characterize pharmacokinetics in the elderly.

In vitro studies demonstrate that terfenadine is extensively (97%) bound to human serum protein while the acid metabolite is approximately 70% bound to human serum protein. Based on data gathered from in vitro models of antihistaminic activity, the acid metabolite of terfenadine has approximately 30% of the H1 blocking activity of terfenadine. The relative contribution of terfenadine and the acid metabolite to the pharmacodynamic effects have not been clearly defined. Since unchanged terfenadine is usually not detected in plasma and active acid metabolite concentrations are relatively high, the acid metabolite may be the entity responsible for the majority of efficacy after oral administration of terfenadine.

In a study involving the oral administration of terfenadine to 24 subjects, mean peak plasma levels of the acid metabolite occurred approximately 2.5 hours after dosing. Plasma concentrations of unchanged terfenadine were not detected. The elimination profile of the acid metabolite was biphasic in nature with an initial mean plasma half-life of 3.5 hours followed by a mean plasma half-life of 6 hours. Ninety percent of the plasma level time curve was associated with these half-lives. Although the elimination profile is somewhat complex, the effective pharmacokinetic half-life can be estimated at approximately 8.5 hours. However, receptor binding and pharmacologic effects, both therapeutic and adverse, may persist well beyond that time.

INDICATIONS AND USAGE

Terfenadine is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

Clinical studies conducted to date have not demonstrated effectiveness of terfenadine in the common cold.

CONTRAINDICATIONS

CONCOMITANT ADMINISTRATION OF TERFENADINE WITH KETOCONAZOLE OR ITRACONAZOLE IS CONTRAINDICATED. TERFENADINE IS ALSO CONTRAINDICATED IN PATIENTS WITH DISEASE STATES OR OTHER CONCOMITANT MEDICATIONS KNOWN TO IMPAIR ITS METABOLISM, INCLUDING SIGNIFICANT HEPATIC DYSFUNCTION, AND CONCURRENT USE OF CLARITHROMYCIN, ERYTHROMYCIN, OR TROLEANDOMYCIN. QT PROLONGATION HAS BEEN DEMONSTRATED IN SOME PATIENTS TAKING TERFENADINE IN THESE SETTINGS, AND RARE CASES OF SERIOUS CARDIOVASCULAR EVENTS, INCLUDING DEATH, CARDIAC ARREST, AND TORSADES DE POINTES, HAVE BEEN REPORTED IN THESE PATIENT POPULATIONS. (See **WARNINGS** and **PRECAUTIONS**: *Drug Interactions*.)

Terfenadine is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

WARNINGS

Terfenadine undergoes extensive metabolism in the liver by a specific cytochrome P450 isoenzyme. This metabolic pathway may be impaired in patients with hepatic dysfunction (alcoholic cirrhosis, hepatitis) or who are taking drugs such as ketoconazole, itraconazole, or clarithromycin, erythromycin or troleandomycin (macrolide antibiotics), or other potent inhibitors of this isoenzyme. Interference with this metabolism can lead to elevated terfenadine plasma levels associated with QT prolongation and increased risk of ventricular tachyarrhythmias (such as torsades de pointes, ventricular tachycardia, and ventricular fibrillation) at the recommended dose. Terfenadine is contraindicated for use by patients with these conditions (See WARNING BOX, CONTRAINDICA-

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Other patients who may be at risk for these adverse cardiovascular events include patients who may experience new or increased QT prolongation while receiving certain drugs or having conditions which lead to QT prolongation. These include patients taking certain antiarrhythmics, bepridil, certain psychotropics, probucol, or astemizole; patients with electrolyte abnormalities such as hypokalemia or hypomagnesemia, or taking diuretics with potential for inducing electrolyte abnormalities; and patients with congenital QT syndrome. Terfenadine is not recommended for use by patients with these conditions.

The relationship of underlying cardiac disease to the development of ventricular tachyarrhythmias while on terfenadine therapy is unclear; none the less, terfenadine should also be used with caution in these patients.

PRECAUTIONS

Information for patients

Patients taking terfenadine should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be advised to take terfenadine only as needed and NOT TO EXCEED THE PRESCRIBED DOSE. Patients should be questioned about use of any other prescription or over-the-counter medication, and should be cautioned regarding the potential for life-threatening arrhythmias with concurrent use of ketoconazole, itraconazole, clarithromycin, erythromycin, or troleandomycin. Patients should be advised to consult the physician before concurrent use of other medications with terfenadine. Patients should be questioned about pregnancy or lactation before starting terfenadine therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children. See Patient Information at end of insert.

Drug Interactions

Ketoconazole

Spontaneous adverse reaction reports of patients taking concomitant ketoconazole with recommended doses of terfenadine demonstrate QT interval prolongation and rare serious cardiac events, e.g. death, cardiac arrest, and ventricular arrhythmia including torsades de pointes. Pharmacokinetic data indicate that ketoconazole markedly inhibits the metabolism of terfenadine, resulting in elevated plasma terfenadine levels. Presence of unchanged terfenadine is associated with statistically significant prolongation of the QT and QTc intervals. **Concomitant administration of ketoconazole and terfenadine is contraindicated** (see **CONTRAINDICATIONS, WARNINGS** and **ADVERSE REACTIONS**).

Itraconazole

Torsades de pointes and elevated parent terfenadine levels have been reported during concomitant use of terfenadine and itraconazole in clinical trials of itraconazole and from foreign post-marketing sources. One death has also been reported from foreign post-marketing sources. **Concomitant administration of itraconazole and terfenadine is contraindicated** (see **CONTRAINDICATIONS, WARNINGS,** and **ADVERSE REACTIONS**).

Due to the chemical similarity of other azole-type antifungal agents (including fluconazole, metronidazole, and miconazole) to ketoconazole and itraconazole, concomitant use of these products with terfenadine is not recommended pending full examination of potential interactions.

Macrolides

Clinical drug interaction studies indicate that erythromycin and clarithromycin can exert an effect on terfenadine metabolism by a mechanism which may be similar to that of ketoconazole, but to a lesser

as needed and NOT TO EXCEED THE PRESCRIBED DOSE. Patients should be questioned about use of any other prescription or over-the-counter medication, and should be cautioned regarding the potential for life-threatening arrhythmias with concurrent use of ketoconazole, itraconazole, clarithromycin, erythromycin, or troleandomycin. Patients should be advised to consult the physician before concurrent use of other medications with terfenadine. Patients should be questioned about pregnancy or lactation before starting terfenadine therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children. See Patient Information at end of insert.

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Due to the chemical similarity of other azole-type antifungal agents (including fluconazole, metronidazole, and miconazole) to ketoconazole and itraconazole, concomitant use of these products with terfenadine is not recommended pending full examination of potential interactions.

Macrolides

Clinical drug interaction studies indicate that erythromycin and clarithromycin can exert an effect on terfenadine metabolism by a mechanism which may be similar to that of ketoconazole, but to a lesser extent. Although erythromycin measurably decreases the clearance of the terfenadine acid metabolite, its influence on terfenadine plasma levels is still under investigation. A few spontaneous accounts of QT interval prolongation with ventricular arrhythmia including torsades de pointes have been reported in patients receiving erythromycin or troleandomycin.

Concomitant administration of terfenadine with clarithromycin, erythromycin, or troleandomycin is contraindicated (see CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS). Pending full characterization of potential interactions, concomitant administration of terfenadine with other macrolide antibiotics, including azithromycin, is not recommended. Studies to evaluate the

potential interaction of terfenadine with azithromycin are in progress

Carcinogenesis, mutagenesis, impairment of fertility

Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 19 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C

There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Terfenadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Terfenadine is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to terfenadine only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use

Safety and effectiveness of terfenadine in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

Cardiovascular adverse events

Rare reports of severe cardiovascular adverse effects have been received which include ventricular tachyarrhythmias (torsades de pointes, ventricular tachycardia, ventricular fibrillation, and cardiac arrest), hypotension, palpitations, syncope, and dizziness. Rare reports of deaths resulting from ventricular tachyarrhythmias have been received (see **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS:** *Drug Interactions*). Hypotension, palpitations, syncope, and dizziness could reflect undetected ventricular arrhythmia. IN SOME PATIENTS, DEATH, CARDIAC ARREST, OR TORSADES DE POINTES HAVE BEEN PRECEDED BY EPISODES OF SYNCOPE. (See **WARNING BOX**). Rare reports of serious cardiovascular adverse events have been received, some involving QT prolongation and torsades de pointes, in apparently normal individuals without identifiable risk factors. There is not conclusive evidence of a causal relationship of these events with terfenadine. Although in rare cases there was measurable plasma terfenadine, the implications of this finding with respect to the variability of terfenadine metabolism in the normal population cannot be assessed without further study. In controlled clinical trials in otherwise normal patients with rhinitis, small increases in QTc interval were observed at doses of 60 mg b.i.d. In studies at 300 mg b.i.d. a mean increase in QTc of 10% (range -4% to +30%) (mean increase of 46 msec) was observed.

General adverse events

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received terfenadine, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving terfenadine was similar to that reported in patients receiving placebo. (See Table below.)

Adverse Event	
Central Nervous System	
	Drowsiness
	Headache
	Fatigue

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Adverse Events Reported in Clinical Trials

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Terfenadine N=781	Placebo N=665	Control N=626***	Terfenadine N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	16.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.8	0.5
Appetite Increase	0.5	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat, Epistaxis					
Skin Eruption (including rash and urticaria) or itching					

* Duration of treatment in "CONTROLLED ST

** Duration of treatment in "ALL CLINICAL ST

*** CONTROL DRUGS: Chlorpheniramine (291 (180 patients), Clemastine (146 patients)

6	3.0	2.7	7.6	5.4
3	1.8	3.5	4.8	3.1
19	0.2	0.5	2.5	1.7

Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

* Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.
** Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.
*** CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of terfenadine that warrant listing as possibly associated with drug administration. These include: alopecia (hair loss or thinning), anaphylaxis, angioedema, bronchospasm, confusion, depression, galactorrhea, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, paresthesia, photosensitivity, rapid flare of psoriasis, seizures, sinus tachycardia, sweating, thrombocytopenia, tremor, urinary frequency, and visual disturbances.

In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving terfenadine. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis. In most cases available information is incomplete.

OVERDOSAGE

Signs and symptoms of overdosage may be absent or mild (e.g., headache, nausea, confusion); but adverse cardiac events including cardiac arrest, ventricular arrhythmias including torsades de pointes and QT prolongation have been reported at overdoses of 360 mg or more and occur more frequently at doses in excess of 600 mg, and QTc prolongations of up to 30% have been observed at a dose of 300 mg b.i.d. Seizures and syncope have also been reported. USE OF DOSES IN EXCESS OF 60 MG B.I.D. IS NOT RECOMMENDED. (See **WARNING BOX, CLINICAL PHARMACOLOGY**, and **ADVERSE REACTIONS**.)

In overdose cases where ventricular arrhythmias are associated with significant QTc prolongation, treatment with antiarrhythmics known to prolong QTc intervals is not recommended.

Therefore, in cases of overdosage, cardiac monitoring for at least 24 hours is recommended and for as long as QTc is prolonged, along with standard measures to remove any unabsorbed drug. Limited experience with the use of hemoperfusion (N=1) or hemodialysis (N=3) was not successful in completely removing the acid metabolite of terfenadine from the blood.

Treatment of the signs and symptoms of overdosage should be symptomatic and supportive after the acute stage.

Oral LD50 values for terfenadine were greater than 5000 mg/kg in mature mice and rats. The oral LD50 was 438 mg/kg in newborn rats.

DOSAGE AND ADMINISTRATION

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Oral LD50 values for terfenadine were greater than 5000 mg/kg in mature mice *and rats. The oral LD50 was 438 mg/kg in* newborn rats.

DOSAGE AND ADMINISTRATION

One tablet (60 mg) twice daily for adults and children 12 years and older.

USE OF DOSES IN EXCESS OF 60 MG B.I.D. IS NOT RECOMMENDED BECAUSE OF THE INCREASED POTENTIAL FOR QT INTERVAL PROLONGATION AND ADVERSE CARDIAC EVENTS. (See **WARNING BOX.**) USE OF TERFENADINE IN PATIENTS WITH SIGNIFICANT HEPATIC DYSFUNCTION AND IN PATIENTS TAKING KETOCONAZOLE, ITRACONAZOLE, CLARITHROMYCIN, ERYTHROMYCIN OR TROLEANDOMYCIN IS CONTRAINDICATED. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS:** *Drug Interactions.*)

HOW SUPPLIED

60mg tablets in bottles of 30's.

60 mg tablets in bottles of 100's.

60 mg tablets in bottles of 500's.

Terfenadine Tablets USP are white, round, unscored, debossed with "6401" on one side and ⧖ logo on the other. Store tablets at controlled room temperature 15°-30°C (59°-86°F). Keep tightly closed. Protect from moisture.

Dispense in a tight, light-resistant container with child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

Prescribing Information as of February 1995.

PATIENT INFORMATION
Terfenadine Tablets USP
60 mg

This leaflet is a summary of important information about terfenadine. Be sure to ask your doctor if you have any questions *or want to know more.*

What Is Terfenadine and What Is It Used For?

Terfenadine is an antihistamine. It is used to relieve symptoms of seasonal allergies or hay fever. These symptoms include runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes.

Clinical studies conducted to date with Terfenadine have not demonstrated effectiveness in relieving the symptoms of the common cold.

How Do I Take Terfenadine?

- Take terfenadine only as needed when you have symptoms of seasonal allergy or hay fever.
- The recommended dose of terfenadine is one tablet taken twice a day. **DO NOT TAKE MORE OFTEN THAN ONE TABLET EVERY TWELVE HOURS.**
- Follow any other instructions your doctor gives you.

What Are The Important Warnings About Using Terfenadine?

WARNING: DO NOT USE TERFENADINE IF YOU ARE USING KETOCONAZOLE (NIZORAL), ITRACONAZOLE (SPORANOX), ERYTHROMYCIN, CLARITHROMYCIN (BIAXIN), OR TROLEANDOMYCIN (TAO). IF YOU HAVE ANY LIVER OR HEART PROBLEMS, TALK TO YOUR DOCTOR BEFORE YOU USE TERFENADINE.

Do not use Terfenadine with any other prescription or nonprescription medicines without first talking to your doctor and pharmacist.

If you faint, become dizzy, have any unusual heartbeats, or any other *unusual* symptoms while using terfenadine, contact your doctor.

If you become pregnant or are nursing a baby, talk to your doctor about whether you should take terfenadine. *Your doctor* will decide whether you should take terfenadine based on the benefits and the risks.

What Are the Risks of Using Terfenadine?

The side effects which occur most often are headaches and mild stomach or intestinal problems.

In rare cases, terfenadine has caused *IRREGULAR HEARTBEATS which may* cause serious problems like fainting, dizziness, cardiac arrest, or death. In these rare cases, this occurred when terfenadine was taken:

- *in more than the recommended* dose (Remember, do not take more often than one tablet every twelve hours.);
- with the antifungal drugs ketocona-

10

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60 mg

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- in more than the recommended dose (Remember, do not take more often than one tablet every twelve hours.);
- with the antifungal drugs ketoconazole (Nizoral) or itraconazole (Sporanox);
- with the antibiotic drugs erythromycin, clarithromycin (Biaxin), or troleandomycin (TAO);
- by patients with serious liver disease.

How Do I Store Terfenadine?

Terfenadine should be stored in a tightly closed container, in a cool place, out of direct sunlight. It should be kept away from children.

Patient Information as of February 1995.

Manufactured by
BAKER NORTON PHARMACEUTICALS, INC.*
Miami, FL 33178

1001025 Rev. 9502

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 0744575

BIOEQUIVALENCE DISSOLUTION REVIEWS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-475 SPONSOR: Baker-Norton
DRUG: Terfenadine
DOSAGE FORM: Tablet
STRENGTH(s): 60 mg
TYPE OF STUDY: (Single)/Multiple (Fasting)/Fed
STUDY SITE:

STUDY SUMMARY: A fasting study was completed in 24 subjects. The ratios of the means were 1.01, 0.97 and 0.99 for the AUC_{0-t}, AUC_{0-inf} and C_{max}, respectively, of terfenadine. The 90% confidence intervals for the $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max} of terfenadine were (0.84; 1.48), (0.79; 1.40) and (0.83; 1.22), respectively. The 90% confidence intervals for the $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max} of carboxyterfenadine were (1.00; 1.14), (0.99; 1.15) and (0.96; 1.12), respectively.

DISSOLUTION: Dissolution tests were conducted in 900 mL of 0.1N HCl, us USP 22 paddle apparatus at 50 rpm. The results are acceptable according to specification recommended by USP of "not less than of labeled amount terfenadine in the dosage form are dissolved in 45 min".

PRIMARY REVIEWER: BRANCH:

INITIAL: L Chang DATE: 5/23/95

BRANCH CHIEF: BRANCH:

INITIAL: DATE: 5/24/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DATE: 5/30/95

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE: 6/18/95

MAY 30 1995

Terfenadine
Tablet, 60 mg
ANDA # 74-475
Reviewer: L. Chuang

Baker Norton Pharmaceuticals, Inc.
Miami, Florida
Submission Date:
December 16, 1994

Review of an amendment to In-Vivo Bioequivalence Studies and Dissolution Data

This amendment was submitted to address the following deficiencies:

1. The information concerning changes made during the amending of protocol on August 23 and November 10, 1993 and the documented IRB approval of these changes should be provided.

   The amendment of August 23, 1993 provided the following changes:

   a. To add "non-smoking" to the inclusion criteria.

   b. To change the 16-hour blood sample after dosing to 18-hour after dosing.

   c. To change the range of volunteers' age from 18-45 years to 21-40 years.

   d. To add electrolytes (Na, Cl, K) to the serum chemistry tests.

   e. To add two exclusion criteria of "subjects who uses tobacco products" and "subjects who have been exposed to known hepatic enzyme inducing or inhibiting agents within 30 days prior to the study".

   f. To change the period of medication restriction from 7 days to 14 days and the period of alcohol- or xanthine-containing beverages and foods restriction from 24 hours to 48 hours.

   g. To indicate the formulation dose of 2 x 60 mg tablets.

   h. To specify the length of time for blood samples to be in the ice bath (at least 1 minute) and the centrifugation time (7 minutes within 12 minutes of sample collection).

   i. To include the source of reference document for

statistical analysis.

The IRB was not informed of these changes because they were considered not affecting the safety of the subjects.

The amendment of November 10, 1993 changed the limit of quantitation for terfenadine from which was the limit of quantitation reported in the original submission. This change did not affect subject safety and therefore the IRB was not notified.

2. The lot size of the test product and the potencies of both test and reference products used in the bioequivalence study should be provided.

The lot size of the test product was

The potency was 100% for the test product and 95% for the reference product.

3. The firm should explain the inconsistency of the clinical study dates (08/27-31/93 and 09/10-14/93) and the blood collection dates (08/28/93 and 11/09/93) for terfenadine analysis .

This was the result of the way reports dates as day/month/year. Therefore 11/09/93 was actually September 11, 1993 not November 9, 1993.

4. The firm should explain the inconsistency of the time period of terfenadine analytical procedure reported in the analytical report section and the raw data section.

This was due to the 6 days period between the last chromatograms were run and the last day the data workup for determination of concentration was made.

5. The dissolution volume, assay methodology used during the dissolution testing, and the coefficients of variation of the amount dissolved at each time point during the dissolution testing should be reported.

The information are provided in the dissolution table below:

In Vitro Dissolution Testing

Drug (Generic Name): Terfenadine Tablets
Dose Strength: 60 mg
ANDA No.: 74-475
Firm: Baker Norton Pharmaceuticals, Inc.

I. Conditions for Dissolution Testing:

USP XXII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: 0.1 N HCL Volume: 900 ml
Tolerance: NLT (Q) in 45 minutes
Reference Drug: Seldane® Tablets (Merrell Dow)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # RD-93047 Strength (mg): 60			Reference Product Lot # P50-491 Strength (mg): 60		
	Mean %	Range	%CV	Mean %	Range	%CV
15	79		2.3	74		0.4
30	86		2.4	85		0.3
45	86		3.2	88		0.2
60	89		1.7	91		0.3

Comments:

1. The only item of the protocol changes that may affect subject safety was the administration of 120 mg of terfenadine. However, serious adverse reactions due to overdose were observed only at 360 mg or more (p1430, PDR, 49th ed, 1995). Therefore, the response to deficiency #1 is acceptable.

2. The explanations for deficiencies #2-#5 provided by the firm are acceptable.

Recommendation:

1. The bioequivalence study conducted by Baker Norton Pharmaceuticals, Inc. on its Terfenadine 60 mg tablet, lot #RD-93047, comparing to Seldane® 60 mg tablet manufactured by Merrell Dow Pharmaceuticals Inc. has been found acceptable by the division of Bioequivalence. The study demonstrated that Baker Norton's terfenadine tablet, 60 mg, is bioequivalent to the reference product, Seldane® 60 mg Tablet manufactured by

Recommendation:

1. The bioequivalence study conducted by Baker Norton Pharmaceuticals, Inc. on its Terfenadine 60 mg tablet, lot #RD-93047, comparing to Seldane® 60 mg tablet manufactured by Merrell Dow Pharmaceuticals Inc. has been found acceptable by the division of Bioequivalence. The study demonstrated that Baker Norton's terfenadine tablet, 60 mg, is bioequivalent to the reference product, Seldane® 60 mg Tablet manufactured by Merrell Dow when administered under fasting condition.

2. The dissolution testing data conducted by Baker Norton Pharmaceuticals, Inc. in its terfenadine tablet, 60 mg, Lot #RD-93047 are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 1N HCl at 37° using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of terfenadine in the dosage form are dissolved in 45 minutes.

L. Chuang

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 5/24/95

Concur: _____ Date: 5/30/95

Keith Chan, ~~Ph.D.~~
Director, Division of Bioequivalence

cc: ANDA 74-475 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Chuang), Drug File, Division File

LWC/052395/dm/WP #74-475am.d94

DIV

Terfenadine Tablets USP, 60 mg
ANDA 74-475

Baker Norton Pharmaceuticals
Attention: Jane Hsiao
8800 Northwest 36th Street
Miami, FL 33178-2404

NOV 16 1994

Dear Dr. Hsiao:

Reference is made to the *in vivo* study and *in vitro* dissolution data submitted on February 25, 1994, for Terfenadine Tablets USP, 60 mg.

The Office of Generic Drugs has reviewed the referenced material and we have the following comments:

A. The bioequivalence study comparing the test product Terfenadine Tablets, 60 mg, lot #RD-93047, manufactured by Baker Norton Pharmaceuticals with the reference listed drug Seldane® Tablets, 60 mg, manufactured by Merrell Dow Pharmaceuticals Inc. is incomplete for the following reasons:

1. The original protocol was amended on August 23 and November 10, 1993. Please provide a summary and an explanation of these changes along with the documented IRB approval of these changes.

2. The following information submitted in the application appears to be inconsistent, and will require an explanation:

   i. The analytical report stated that the dates of blood sample collection were during August 28 and November 9, 1993.

   ii. The clinical study, which included blood collection, was conducted August 27, 1993 through August 31, 1993 and September 10, 1993 through September 14, 1993.

   iii. The last sample analysis for terfenadine was reported as November 12, 1993, while the last day of analysis in the raw data section is reported as November 18, 1993.

3. The lot size of the test product and the potencies of both test and reference products used in the *in vivo* bioequivalence study should be provided.

B. The dissolution testing conducted on the test product Terfenadine 60 mg tablets, lot #RD-93047, manufactured by Baker Norton Pharmaceuticals, Inc. is incomplete for the following reasons:

The dissolution volume, assay methodology used during the dissolution testing, and the coefficients of variation of the amount dissolved at each time point during the dissolution testing should be reported. Please submit the required information for review.

You are required to take an action described under 21 CFR 314.96 which will amend this application.

Representatives of the Division of Bioequivalence are available to discuss this letter and to assist you. Please contact Jason A. Gross, Pharm. D. at (301) 594-0317 for further assistance.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

OCT 28 1994

DIV

Terfenadine
Tablet, 60 mg
ANDA # 74-475
Reviewer: L. Chuang
WP#74475SD.294

Baker Norton Pharmaceuticals, Inc.
Miami, Florida
Submission Date:
February 25, 1994

Review of In-Vivo Bioequivalence Studies and Dissolution Data

Introduction:

Terfenadine is a histamine H_1 receptor antagonist. It is indicated for the relief of symptoms associated with seasonal allergic rhinitis. The frequency of drowsiness with terfenadine was similar to the frequency with placebo, and less than that with other antihistamines. The frequency of anticholinergic effects was not different from that of other antihistamines.

After oral administration, terfenadine undergoes extensive (99%) first pass metabolism to two primary metabolites, an acidic and a dealkylated metabolite. The acid metabolite, carboxyterfenadine, is believed to account for at least one-third of the activity of terfenadine.

Peak plasma concentrations of terfenadine occur 1 to 2 hours after oral administration. The plasma concentration-time curve of the drug follows a biexponential pattern. The distribution and terminal elimination half-lives are 3-4 hours and 16-22 hours respectively. The reported half-lives of the acid metabolite, carboxyterfenadine, vary from 2-3 hours to 17 hours.

Terfenadine is commercially available as 60 mg tablet, Seldane, manufactured by Merrell Dow.

Bioequivalence Study:

The objective of this study is to compare the single-dose bioavailability of the test product and Seldane 60 mg tablet, manufactured by Merrell Dow, following the administration of a 120 mg dose.

The study, both clinical and analytical procedures, was conducted at

The clinical study was conducted during August 27-31 and September 10-14, 1993 with as the supervisor. The analytical report, written by stated that the analysis of terfenadine was conducted during October 21-November 12, 1993 and the analysis of carboxyterfenadine during September 20-October 13, 1993.

The design is a single-dose, 2-way crossover of 2x60 mg of the firm's terfenadine tablet and 2x60 mg of Seldane tablet in fasting volunteers. The
approved the original protocol and the informed consent form on June 22, 1993 and the changes to exclude 2 subjects and add 1 alternate on September 8, 1993. However, no IRB approval documents were included for the amendments made on August 23, 1993 and November 10, 1993.

Twenty-six (26) non-smoking men, 18-37 years old, weighing at least 60 Kg and within ±10% of their ideal weight were recruited. The screening procedures included a physical examination, EKG, and the laboratory tests for hematologic, hepatic and renal functions. Only subjects with normal results were enrolled.

Volunteers with history of alcoholism or drug abuse within the last year, hypersensitivity to terfenadine or any other H_1-receptor antagonist, epilepsy, glaucoma, asthma or urinary difficulties were excluded. Subjects who had been on an abnormal diet during the 4 weeks preceding the study, who through the completion of the study would have donated in excess of 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in 1 year, who had completed another clinical trial within 28 days of study initiation, who used tobacco products or who had been exposed to known haptic enzyme inducer or inhibitor within 30 days of study initiation were also excluded from the study.

All 26 subjects were instructed not to take any drugs for two weeks preceding study initiation, and not to consume any alcohol- or xanthine-containing beverage and food for 48 hours before dosing and during blood sample collection period.

All subjects were fasted overnight before and 4 hours after receiving one of the following randomly assigned drug treatments :

Treatment A - Test Drug: Terfenadine tablets, 2 x 60 mg, Baker Norton Pharmaceuticals Inc., lot #RD93047-01, potency and lot size not given.

Treatment B - Reference Drug: Seldane^R tablet, 2 x 60 mg, Merrell Dow, lot #P50491, expires at 01/96, Potency not given.

Each treatment was taken with 240 mL of water. Blood samples were drawn into heparinized Vacutainers at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 18, 24, 30, 36 (1 x 5 mL and 1 x 10 mL each) 48, 60 and 72 (1 x 10 mL each) hours. The blood samples collected after 36 hours would be assayed only for terfenadine and the blood

samples collected from predose until 36 hours would be assayed for both terfenadine and carboxyterfenadine.

All subjects were confined from 12 hours before dosing until after the 36 hour blood draw and returned for the 48, 60 and 72 hour blood draws. For subjects' safety. their EKGs before dosing and 3 hours after dosing were recorded.

Plasma samples were prepared within 16 minutes and stored at -80°C until analysis. The washout period between the administration of two formulations was 14 days.

Analytical Method:

Results:

Of the 26 subjects, 24 completed the study. Subjects #14 and #22 (both were assigned the treatment sequence of AB) were caught smoking and violated the protocol. One additional subject (#27) was enrolled and completed only period 2 of the study. The data of subject #27, however, was not used in the analysis. The safety monitoring did not encounter any safety problems.

Thirty-three (33) events of adverse reactions were reported. The adverse reactions included loose stool, stomach cramps, dizziness, fainting, sweating, headache,stomach pain, nasal congestion, feeling faint, feeling cold, flatulence and loss of appetite. Thirteen (13) of these events occurred during treatment A and 20 during treatment B. No medication was required for any of these events.

The mid- and post-study laboratory tests results were judged by the medical director to be within normal limits or not clinically significant.

The plasma samples from 24 subjects were assayed for both carboxyterfenadine and terfenadine.

Terfenadine:

It was stated in the analytical report that the dates of blood sample collection were during August 28 and November 9, 1993, however, the clinical study was conducted during August 27-31 and September 10-14, 1993.

Another discrepancy was that the firm reported the date of last sample analysis for terfenadine as November 12, 1993 while the last day of analysis shown in the raw data section was November 18,

1993.

A total 912 study samples were expected from the protocol, but 910 were analyzed, subject #18, hour 72, period 1 (treatment B) and subject #10, hour 60, period 2 (treatment B) were not received by the analytical laboratory. Eighteen (18) standard curves were run with the analysis of study samples, 9 samples were reassayed for terfenadine due to suspected pharmacokinetic outlier. Five (5) of them had the median values reported as their final concentrations, 1 had the original value reported and 3 were 'not reportable'. The 3 'not reportable' samples, subject #1, period 1, 0 hour and subject #25, period 1 and period 2, hour 30, were all in the range of "below limit of quantitation' in the time-concentration curve.

The mean plasma concentrations of terfenadine at each sampling point after both treatments in 24 subjects and the mean pharmacokinetic parameters are presented below in Table 1. Elimination constants used to estimate AUC_{0-inf} were calculated by linear least-square regression analysis using the last 3 (or more) non-zero plasma concentrations. Data from subject #20, treatment A and subjects #18 & 21, treatment B, displayed pharmacokinetic anomaly and the elimination constants, under these circumstances, were unable to be estimated. Five (5) subjects each druing treatment a and treatment B had observed T_{max} of 0.5 hour (the first post-dose blood draw).

Table 1

Mean (C.V.%) Plasma Terfenadine Concentrations (pg/mL) at Each Sampling Time Point and Arithmetic Means of Pharmacokinetic Parameters (n = 24*)

Time (hours)	Baker Norton (Treatment A)	Merrell Dow (Treatment B)
0	0	0
0.5	1070.36 (74)	954.69 (65)
1.0	1557.55 (63)	1323.02 (64)
1.5	1312.51 (67)	1174.48 (63)
2.0	1122.48 (63)	1087.40 (63)
2.5	1065.88 (65)	1076.26 (72)
3.0	972.76 (68)	960.65 (75)
3.5	917.71 (65)	979.98 (76)
4.0	843.25 (68)	902.30 (78)
6.0	898.17 (70)	1006.62 (100)
8.0	724.12 (66)	795.25 (88)
12.0	527.53 (75)	559.05 (93)
18.0	301.73 (82)	327.70 (91)
24.0	253.38 (91)	253.61 (92)
30.0	236.70[a] (96)	206.35[a] (94)
36.0	176.68 (103)	158.41 (100)
48.0	91.23 (108)	82.72 (117)
60.0	62.69 (109)	53.27[a] (121)
72.0	18.37 (215)	23.55[a] (179)
AUC_{0-t} (pg*hr/mL)	19636.6 (73)	19692.3 (84)
AUC_{0-inf} (pg*hr/mL)	21660.4[a] (69)	22244.3[b] (79)
C_{max} (pg/mL)	1673.99 (57)	1688.38 (63)
T_{max} (hr)	1.500 (117)	1.896 (91)
$T_{1/2}$ (hr)	15.887[a] (30)	14.663[b] (43)

* : unless otherwise indicated
a : n = 23
b : n = 22

Analysis of Variance was performed on all pharmacokinetic parameter and the log transformed parameters using SAS GLM procedure. There are no significant difference between periods, sequences and treatments for any of the transformed and untransformed parameters. The LS means of AUC_{0-t}, AUC_{0-inf}, C_{max}, $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} and ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 2.

Table 2

Statistical Analysis -- Terfenadine

Parameter	LS Means Baker Norton	LS Means Merrell Dow	T/R	90% Confidence Interval
AUC_{0-t} (pg*hr/mL)	19545.1	19340.2	1.01	(0.738; 1.283)
AUC_{0-inf} (pg*hr/mL)	21000.0	21691.7	0.97	(0.683; 1.254)
C_{max} (pg/mL)	1667.62	1678.90	0.99	(0.805; 1.182)
$LNAUC_{0-t}$	9.63095	9.52022	1.11	(0.845; 1.477)
$LNAUC_{0-inf}$	9.72487	9.68013	1.05	(0.786; 1.398)
LNC_{max}	7.24460	7.23867	1.01	(0.831; 1.218)

Comments:

1. The 90% confidence intervals of both $LNAUC_{0-t}$ and $LNAUC_{0-inf}$ are not within the 80-125% limits.

2. The confidence interval of LNC_{max} is within the 80-125% limits.

3. The test/reference ratio for all three parameters, log transformed or untransformed, are within the 0.80-1.20 limit.

4. According to the memo of 08/25/94 from Bob Pollock, Acting Deputy Director, OGD, the approval of terfenadine application should be based on a 90% confidence interval for the metabolite and a point estimate on the parent compound.

5. The blood sample collection dates were inconsistent with the clinical study dates.

6. The time period of analytical procedure reported was inconsistent in the analytical report section and in the raw data section.

Carboxyterfenadine

A total 768 study samples were expected from the protocol and all 768 samples were received and analyzed. Fifteen (15) standard curves were run with the analysis of study samples, 4 samples were reassayed for carboxyterfenadine due to suspected pharmacokinetic outliers. Each of these 4 samples was repeated twice and the median value of the 3 results was reported as the final concentration.

The mean plasma concentrations of carboxyterfenadine at each sampling point after both treatments in 24 subjects and the mean pharmacokinetic parameters are presented below in Table 3. Elimination constants used to estimate AUC_{0-inf} were calculated by linear least-square regression analysis using the last 3 (or more) non-zero plasma concentrations. Data from subjects #8, 13 & 24, treatment A and subjects #1, 2, 10, 13, 18 & 25, treatment B, displayed pharmacokinetic anomaly and the elimination constants, under these circumstances, were unable to be estimated.

Table 3

Mean (C.V.%) Plasma Carboxyterfenadine Concentrations (ng/mL) at Each Sampling Time Point and Arithmetic Means of Pharmacokinetic Parameters (n = 24)

Time (hours)	Baker Norton (Treatment A)		Merrell Dow (Treatment B)	
0	0		0	
0.5	71.68	(62)	77.81	(79)
1.0	305.82	(38)	311.53	(28)
1.5	414.68	(27)	423.78	(26)
2.0	474.78	(27)	471.50	(32)
2.5	538.75	(26)	503.97	(27)
3.0	524.98	(28)	498.55	(26)
3.5	510.82	(32)	465.77	(27)
4.0	476.71	(31)	424.08	(26)
6.0	300.11	(39)	258.32	(32)
8.0	166.58	(45)	157.72	(33)
12.0	68.85	(36)	65.70	(26)
18.0	30.70	(32)	28.51	(29)
24.0	19.62	(21)	18.52	(28)
30.0	14.71	(39)	12.54	(63)
36.0	8.93	(93)	7.01	(107)
AUC_{0-t} (ng*hr/mL)	3862.3	(27)	3585.8	(21)
AUC_{0-inf} (ng*hr/mL)	4290.1[a]	(26)	3787.6[b]	(21)
C_{max} (ng/mL)	573.53	(27)	551.72	(24)
T_{max} (hr)	2.604	(23)	2.783	(23)
$T_{1/2}$ (hr)	15.715[a]	(30)	12.795[b]	(63)

* : unless otherwise indicated
a : n = 21
b : n = 18

Analysis of Variance was performed on all pharmacokinetic parameter and the log transformed parameters using SAS GLM procedure. There are no significant difference between periods, sequences and treatments for any of the transformed and untransformed parameters. The LS means of AUC_{0-t}, AUC_{0-inf}, C_{max}, $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} and ratio of these means and the 90% confidence intervals of test product versus reference product are presented in Table 4.

Table 4

Statistical Analysis -- Carboxyterfenadine

Parameter	LS Means Baker Norton	LS Means Merrell Dow	T/R	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	3862.62	3572.07	1.08	(1.011; 1.152)
AUC_{0-inf} (ng*hr/mL)	4215.99	3935.81	1.07	(0.994; 1.148)
C_{max} (ng/mL)	574.16	550.61	1.04	(0.956; 1.130)
$LNAUC_{0-t}$	8.22515	8.15894	1.06	(1.004; 1.137)
$LNAUC_{0-inf}$	8.31493	8.25041	1.07	(0.988; 1.151)
LNC_{max}	6.32039	6.28523	1.06	(0.959; 1.119)

Comments:

1. The confidence interval of all log transformed parameters are within the limit of 80-125%.

2. According to the memo of 08/25/94 from Bob Pollock, Acting Deputy Director, OGD, the approval of terfenadine application should be based on a 90% confidence interval for the metabolite and a point estimate on the parent compound.

Dissolution Testing:

The firm has submitted dissolution data on its Terfenadine tablet, 60 mg, lot #RD-93047, compared to the reference product, Seldane® tablet, 60 mg, lot #P50491. The method and results are presented in Table 5.

Table 5. In-Vitro Dissolution Testing- Terfenadine 60 mg Tablet

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle XX RPM 50 No. Units Tested: 12
Medium: 0.1 N HCl Volume: Not Given ml
Reference Drug: (Manuf.) Seldane® tablet, 60 mg, (Merrell Dow)
Assay Methodology: Not Given

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min)	Test Product			Reference Product		
	Mean % Dissolved	Range	(%CV)	Mean % Dissolved	Range	(%CV)
	Lot # RD-93047 Strength: 60 mg			Lot # P50491 Strength: 60 mg		
15	79		(---)	74		(---)
30	86		(---)	85		(---)
45	86		(---)	88		(---)
60	89		(---)	91		(---)

Comment:

The firm did not provide the amount of dissolution volume, the assay methodology and coefficient of variation of the amount dissolved at each sampling point.

The quantitative composition of the test product is listed below in Table 6:

Table 6: Quantitative Composition of Terfenadine 60 mg Tablet Manufactured by Baker Norton Pharmaceuticals, Inc.

Ingredient	Weight (mg) /Tablet	Percentage (%)
Terfenadine	60	10.9
Lactose Monohydrate		
Starch		
Providone		
Sodium Bicarbonate		
Ethyl Alcohol		
Magnesium Stearate		
Total	550	100.0

* = Removed during processing

Deficiencies:

1. The information concerning changes made during the amending of protocol on August 23 and November 10, 1993 and the documented IRB approval of these changes should be provided.

2. The lot size of the test product and the potencies of both test and reference products used in the bioequivalence study should be provided.

3. The firm should explain the inconsistency of the clinical study dates (08/27-31/93 and 09/10-14/93) and the blood collection dates (08/28/94 and 11/09/93) for terfenadine analysis .

4. The firm should explain the inconsistency of the time period of terfenadine analytical procedure reported in the analytical report section and the raw data section.

5. The dissolution volume, assay methodology used during the dissolution testing, and the coefficients of variation of the amount dissolved at each time point during the dissolution testing should be reported.

Recommendation:

1. The bioequivalence study conducted by Baker Norton Pharmaceuticals, Inc. on its Terfenadine 60 mg tablet, lot #RD-93047, comparing to Seldane® 60 mg tablet manufactured by Merrell Dow Pharmaceuticals Inc. has been found incomplete by the Division of Bioequivalence. The firm should clarify the Deficiencies 1-4.

2. The dissolution testing conducted by Baker Norton Pharmaceuticals, Inc. on its Terfenadine 60 mg tablets, lot #RD-93047, has been found incomplete due to deficiency #5.

The above comments, deficiencies and recommendation should be forwarded to the firm.

Lin-whei Chuang

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED AJACKSON
FT INITIALED AJACKSON

Concur: _____ Date: 10/28/94
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-475 original, HFD-630, HFD-600 (OGD, Hare), HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-652 (Chuang, Jackson), Drug File.

LC/101994/ntp/WP#74475SD.294